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## Ovarian cancer Symptoms are not early signs of ovarian cancer

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## OVARIAN CANCER

### Usefulness of abdominal symptoms in early diagnosis



STEVE GSCHEISSNER/SPL

In contrast to the predictable media coverage of Hamilton and colleagues' claims about early detection of ovarian cancer,<sup>1</sup> general practitioners are crying out for reliable information on the predictive value of symptoms to enable early diagnosis and select patients for further investigation.

One surprising omission from the study is a review of the community prevalence of the symptoms investigated. The prevalence of abdominal bloating in the control subjects was 2% (21 out of 1060 subjects). General practitioners active in clinical practice will find this surprisingly low, community surveys estimating it to be 16-30%.<sup>2</sup> The positive predictive value for abdominal bloating that the authors calculate (0.3%) will be much lower if the prevalence of bloating is greater than the 2% in their controls.

They state: "Women with ovarian cancer usually have symptoms and report them to primary care, sometimes months before diagnosis." But they found that women with ovarian cancer have the same variety of non-specific symptoms that many women experience, that some of these symptoms (abdominal pain, distension, and loss of appetite) are substantially more common in the two or three months before diagnosis, and that one symptom (abdominal bloating) is more common for longer than this, but only compared with the surprisingly low prevalence in their controls. All of this makes their final rather emotive claim—"ovarian cancer is not silent, rather its sound is going unheard"—and their comments to an unsceptical media rather surprising.

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Competing interests: None declared.

- 1 Hamilton W, Peters TJ, Bankhead C, Sharp D. Risk of ovarian cancer in women with symptoms in primary care: population based case-control study. *BMJ* 2009;339:b2998. (25 August.)
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### Symptoms are not early signs of ovarian cancer

Hamilton and colleagues detected significant associations between bloating and increased abdominal distension and diagnosis of ovarian cancer,<sup>1</sup> but these symptoms are not early signs of ovarian cancer but of advanced stage disease: an enlarged ovary, omental cake, or ascites. Visiting a doctor will result in diagnosis but not improved prognosis.

Bloating and abdominal distension are non-specific signs. Almost every woman has them in the second half of the menstrual cycle, and women with irritable bowel syndrome experience them frequently if not daily. As most women will not visit their general practitioners for these symptoms, this study cannot be regarded as population based.

Giving prominence to these non-specific signs and referring women to a gynaecologist for ultrasonography is not likely to be cost effective and will increase anxiety about cancer. On the basis of these results, abdominal distension and abdominal pain will yield, respectively, an additional 14 and 217 referrals yearly for each general practitioner. A prospective trial is needed to see whether such referrals result in earlier diagnosis of ovarian cancer.

We have more than 15 years' experience in screening for ovarian cancer in a high risk population. Even with annual gynaecological screening and the possibility of visiting a doctor sooner if there are symptoms, we can only diagnose ovarian cancers at an advanced stage (IIIC).<sup>2</sup> Therefore, instead of investing in late and non-specific signs and symptoms without proved efficacy in reducing mortality from ovarian cancer, we recommend investing in research on biomarkers to detect ovarian cancer at an early stage.

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Competing interests: None declared.

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## BRAN AND IRRITABLE BOWELS

### Bran's deleterious effects: much ado about nothing

Bijkerk and colleagues' randomised controlled trial of soluble and insoluble fibre supplementation in irritable bowel syndrome is the first to be conducted entirely in primary care.<sup>1</sup>

In a systematic review and meta-analysis of trials in specialist settings, our group reported a beneficial effect of soluble fibre in the form of psyllium (or ispaghula husk) in irritable bowel syndrome with a number needed to treat (NNT) of 6 (95% confidence interval 3 to 50).<sup>2</sup> Insoluble fibre in the form of bran was of no benefit, though we could not examine any potentially deleterious effect on symptoms suggested by some investigators<sup>3</sup> because of the way in which data were reported. In Bijkerk and colleagues' trial, the high dropout rates at 12 weeks meant that the effects of ispaghula on abdominal pain or discomfort were only modest, but when these data were incorporated into our meta-analysis the NNT was similar (7 (4 to 25)).

Bijkerk and colleagues say that "bran showed no clinically relevant benefit, and many patients seemed not to tolerate bran." However, the numerical difference was not significant. After 12 weeks, abdominal pain and discomfort were better with bran than either ispaghula or placebo in both the intention to treat and worst case analysis, and symptom severity scores for irritable bowel syndrome improved compared with placebo.

Some patients with irritable bowel syndrome in primary care thus seem to respond to insoluble fibre supplementation. Further study of its utility in a subgroup of patients therefore seems to be warranted.



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**Competing interests:** None declared.

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## ROSIGLITAZONE AND PIOGLITAZONE

### Beware fractures

Juurlink and colleagues show that pioglitazone has fewer adverse cardiovascular outcomes than rosiglitazone, which may be a class effect.<sup>1</sup> However, recent reports show that thiazolidinediones are associated with increased incidence of fractures.

By 2007 the manufacturers of pioglitazone had advised health professionals about the risk of fractures in women on the basis of clinical trial data outcomes.<sup>2</sup> Recent reports show that both men and women who take thiazolidinediones for diabetes could be at increased risk of distal fractures of upper and lower limbs,<sup>3-5</sup> the risk increasing with age.

The black box warning from the US Food and Drug Administration a few years after the introduction of thiazolidinediones, the withdrawal of troglitazone because of rare cases of severe hepatotoxicity, and the increased risk of fractures have raised concerns. Do the benefits of treatment outweigh the risks? Are thiazolidinediones the treatment of choice for type 2 diabetes?

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**Competing interests:** None declared.

- 1 Juurlink DN, Gomes T, Lipscombe LL, Austin PC, Hux JE, Mamdani MM. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. *BMJ* 2009;339:b2942. (18 August.)
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## INTERVENTIONS AND KNEE PAIN

### When knee pain is not osteoarthritis

Jenkinson and colleagues show that a simple dietary and exercise intervention has positive effects on knee pain.<sup>1</sup> Over half of their unselected group, however, did not have radiological evidence of osteoarthritis. This shows that practitioners should always consider intra-articular and periarticular soft tissue problems and referred pain from other musculoskeletal regions. This large group might have a range of potentially self limiting soft tissue disorders skewing the observed improvements. This could be determined by interim analysis of WOMAC pain scores and functioning in those with low Kellgren-Lawrence scores at six or 12 months, thus identifying the characteristics of a better prognostic group.

In such a varied group, how is a poorer prognostic group defined? The authors have previously examined the role of muscle power and knee pain,<sup>2</sup> muscle strength being significantly higher in the exercise group, although baseline values were not presented.<sup>3</sup> Higher WOMAC pain scores and lower muscle strength might be expected in the group with higher radiographic scores, but this caveat may not necessarily hold true. Furthermore, muscle weakness may initiate and perpetuate the progression of osteoarthritis,<sup>4</sup> so to target muscle strength<sup>5</sup> and weight loss in the group with low pain scores and evident radiographic change may be a worthwhile preventive strategy.

This brief intervention strategy would be implemented in primary care or outpatient clinics. In a fashion akin to salivary thiocyanate assays in smokers, could a quick bedside measure of extensor strength be a modifiable and predictive surrogate for compliance with an exercise programme alongside traditional measures such as weight and blood pressure?

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**Competing interests:** None declared.

- 1 Jenkinson CM, Doherty M, Avery AJ, Read A, Taylor MA, Sach TH, et al. Effects of dietary intervention and quadriceps strengthening exercises on pain and function in overweight people with knee pain: randomised controlled trial. *BMJ* 2009;339:b3170. (18 August.)
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## SARCOIDOSIS

### Technique to enable diagnosis

Conventional flexible bronchoscopy is of limited yield in diagnosing sarcoidosis when central or peripheral airways are not affected.<sup>1</sup> However, endobronchial ultrasound guided transbronchial needle aspiration may be helpful in patients with clinical sarcoidosis and computed tomographic evidence of accessible mediastinal nodes. We have confirmed the diagnosis of sarcoidosis using this technique, obviating the need for mediastinoscopy in seven out of nine such cases (table).

Positive histology was regarded as the presence of non-caseating granulomas with negative results in fungal and mycobacterial stains and cultures, and supportive clinical findings with no other clinical explanation for the granulomas. Chest computed tomograms in all cases showed mediastinal nodes with sarcoid-like changes without accessible parenchymal infiltrates or evidence of endobronchial involvement.

#### Details of nine cases of suspected sarcoidosis with mediastinal nodes undergoing EBUS-TBNA

Case No	Nodal stations	Size of node (cm)	Histology
1	7	2	Non-caseating granulomas
2	7	2	Non-caseating granulomas
3	4R, 7	2.5	Non-caseating granulomas
4	3, 7, 10R	2	Non-caseating granulomas
5	7, 10R, 10L	3	Non-caseating granulomas
6	7, 10R	4	Non-caseating granulomas
7	7, 10R	3	Non-caseating granulomas
8	4L	2	Lymphocytes
9	4R	3	Lymphocytes

EBUS-TBNA=endobronchial ultrasound guided transbronchial needle aspiration.

Our findings are supported by several studies showing sensitivities of between 83% and 93% for endobronchial ultrasound guided transbronchial needle aspiration, as well as its superiority over other techniques for stage 1 sarcoid, particularly conventional transbronchial needle aspiration.<sup>2-5</sup> It may be a reasonable and cost effective treatment of choice for patients with suspected sarcoidosis with mediastinal lymphadenopathy in whom transbronchial biopsy or endobronchial biopsy are unlikely to be fruitful.

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**Competing interests:** None declared.

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## FROM SICK NOTES TO FIT NOTES

### Bridging the chasm

As a former manager in a multinational manufacturing company, I find the concept of a fit note laudable.<sup>1</sup> As a medical student currently on elective in occupational health, I can see the resources and knowledge required to make it work is more like bridging a chasm than a gap.

Most of the employers I have spoken to are frustrated with the current sick note system and general practitioners' readiness to sign people off. Most of the general practitioners I have spoken to are frustrated that they don't know enough about a patient's work content or work environment to do otherwise. This knowledge gap is not surprising—most medical students do not study occupational health—but it should be rectified. Some excellent postgraduate courses are available, but only one (at Manchester) allows distance learning. Perhaps the government should encourage general practitioners to complete courses and enter into appropriate dialogue with their patients' employers.

A new referral system to an occupational health service is indeed useful.<sup>1</sup> Most larger employers already buy in these services, and

general practitioners may not be aware that they could refer their patients (with consent) should they have any doubts about the patient's capabilities.

The combined resources of NHS and private occupational health services would not meet the demand generated by introducing fit notes. Challenges include promoting the specialty; providing adequate training places, almost certainly with the help of the private sector; ensuring availability of postgraduate courses; and providing help for small businesses to appreciate the benefits.

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**Competing interests:** None declared.

- 1 Verbeek J, Madan I. From sick notes to fit notes. *BMJ* 2009;339:b3114. (10 August.)

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### Not a simple answer

Fit notes look simple but are likely to be problematic for employers, employees, and general practitioners.<sup>1</sup>

I have been a general practitioner since 1974 and a part-time factory medical officer for the main local employer for over 20 years. Knowing the nature of my patients' tasks at work makes advising on returning to work after sick leave much easier and more useful. In the occupational health department I can advise on graded work to enable return to full function in the shortest time—to the benefit of employees and employer. Knowing all the local general practitioners, I can advise them, subject to consent, how to help their patients to return to work as early as possible. Departmental managers usually accommodate any initial restrictions or arrange alternative work if available, and occupational health nurses are invaluable supportive.

This set-up is not widely available. For general practitioners to issue fit notes seems simplistic if they do not have training in occupational health and do not know what their patients' work entails. Employers and general practitioners will easily become frustrated without advice from occupational health. Fit notes might be better issued by occupational physicians, perhaps with referral from general practitioners. But are there enough professionals trained in occupational health?

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## ASBESTOS AND THE LUNG

### Diffuse pleural thickening has new definition for claims



**Unilateral obliteration of right hemi-diaphragm with diaphragmatic calcification on the right and pleural plaques (large one on the left)**

Currie and colleagues define diffuse pleural thickening in a chest radiograph as “a smooth continuous pleural density affecting 25% of the lateral chest wall, with or without blunting of the costophrenic angle.”<sup>1</sup>

The definition was changed by the Department for Work and Pensions for the purposes of industrial injuries disability benefit for prescribed disease D9 in July 2005, and was passed by parliament in April 2006. It is currently “unilateral or bilateral diffuse pleural thickening with obliteration of the costophrenic angle.”<sup>2</sup> Previously it was pleural thickening (of 5 mm or more in a standard chest radiograph) covering 25% or more of the combined area of the chest wall of both lungs if bilateral, or 50% or more if unilateral.<sup>2</sup>

Although computed tomography may be used to further substantiate a claim, compensation is usually awarded on the basis of standard chest radiography alone and the extent of respiratory disability. The rules for disability claims for asbestos related lung cancer also changed in April 2006.<sup>3</sup>

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## A/H1N1 FLU PANDEMIC

## Managing neutropenic sepsis

The fever of flu may mimic neutropenic fever. Therefore a policy for managing fever during the A/H1N1 flu pandemic in patients with cancer who are receiving chemotherapy has been developed with detailed advice from Professor Nick Phin and Dr Hongxin Zhao of the Health Protection Agency.

Patients receiving chemotherapy who develop a fever should telephone the emergency number of their haematology or oncology unit for advice, not the National Pandemic Flu Service.<sup>1</sup>

If assessed in hospital, patients should wear a surgical mask and be seen in a single room by healthcare professionals using personal protective equipment. A virological swab should be taken and biochemical tests ordered in addition to the usual tests. Other identified causes of fever with a normal or raised neutrophil count should be treated as appropriate.

Patients who are not neutropenic and may have flu should be sent home with a course of oseltamivir, given at the point of contact with the hospital and with advice to self isolate and to take general respiratory and personal hygiene measures.

Patients with neutropenia should be admitted with institution of infection control measures. The microbiologist should be informed, and the neutropenia treated according to the usual protocol with the addition of oseltamivir.

Patients with laboratory confirmed A/H1N1 pandemic flu whose condition does not improve or deteriorates with antiviral treatment should telephone their unit's emergency telephone number. They should attend for reassessment, including a repeat blood count, cultures, and a viral swab. Some of the material should be sent to a laboratory that can detect antiviral resistance. Zanamivir by inhalation should be considered after consultation with a microbiologist or virologist, whether or not the patient is neutropenic.

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Competing interests: None declared.

- 1 Elliot AJ, Powers C, Thornton A, Obi C, Hill C, Simms I, et al. Monitoring the emergence of community transmission of influenza A/H1N1 2009 in England: a cross sectional opportunistic survey of self sampled telephone callers to NHS Direct. *BMJ* 2009;339:b3403. (27 August.)

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## A/H1N1 and other viruses affecting cystic fibrosis

For over 12 months all patients attending our regional cystic fibrosis unit have had throat swabs analysed routinely for viruses with the

polymerase chain reaction before starting intravenous antibiotics. We assessed the prevalence of A/H1N1 flu virus<sup>1</sup> in acute severe exacerbations of cystic fibrosis.

The first case of A/H1N1 flu in Leeds was confirmed on the 7 June 2009. Since then, 187 adult patients have had pulmonary exacerbations requiring intravenous antibiotics. Fifteen had positive viral swabs. Four of them tested positive for A/H1N1 flu virus, one of whom was immunosuppressed after lung transplantation and presented with fever, breathlessness, vomiting, and headache. Eight patients were positive for rhinovirus, two for adenovirus, and one for parainfluenza virus. Repeat swabs remained positive in two patients with A/H1N1 flu virus four and six weeks later.

A/H1N1 flu virus has caused only a few acute pulmonary exacerbations of cystic fibrosis. If the prevalence of viral infections was similar in the community, antiviral drugs are likely to have been overprescribed and people might decline vaccination because they believe that they have already had the infection. Prolonged infection in at risk patients needs further investigation<sup>2</sup> but shows the importance of vaccination in vulnerable groups.

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Competing interests: None declared.

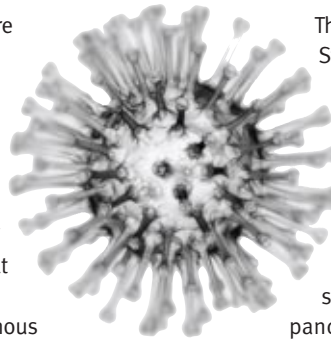
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## By any maths would be as weak

Information from New Zealand and New York City seems to show that 20 000-30 000 people are infected with this pandemic construct for each death.<sup>1-3</sup>

Approximately 3000 deaths have been confirmed,<sup>4</sup> suggesting that between 60 million and 90 million people have already been infected by the 2009 H1N1 pandemic flu virus.



The 595 deaths<sup>5</sup> in the United States equates to 12 million to 18 million infections in the US alone.

By any measure A/H1N1 is a benign flu virus. According to official statements, New Zealand, for example, usually has 400 deaths from flu each year. This year there were 17,<sup>2</sup>

so it could be argued that the pandemic has resulted in 383 lives being saved, which makes it more effective than any flu vaccine.

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Competing interests: None declared.

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## DRUG PREVENTION OF HYPERTENSION

## Contradicting Cochrane

Law and colleagues' conclusion that "drugs are offered to people of all levels of blood pressure" seems to contradict that of a more recent Cochrane review on blood pressure targets for the treatment of hypertension.<sup>1</sup> This systematic review, which seems to consider the same data as Law and colleagues, concludes: "Treating patients to lower than standard blood pressure targets,  $\leq 140$ -160/90-100 mm Hg, does not reduce mortality or morbidity. Because guidelines are recommending even lower targets for diabetes mellitus and chronic renal disease, we are currently conducting systematic reviews in those groups of patients."<sup>2</sup>

As generalists, we find these conflicting conclusions disturbing. Who is right?

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Competing interests: None declared.

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